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## A SYNDROME RESEMBLING HOMOLOGOUS DISEASE AFTER SHORT-TERM CROSS-CIRCULATION IN RABBITS

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Experiments on cross circulation in rabbits have been performed by us since the beginning of 1963. The purpose of these experiments has been to cause immunological denaturation by the administration of large doses of antigen (in this instance whole blood) as a preliminary step in organ transplantation and to investigate the possibilities of clinical application of cross circulation in order that a particular diseased organ may recover its function.

Cross circulation of about two hours' duration has been performed in one hundred (50 pairs) rabbits up to the present and the longest period of observation has been one year. The majority of the rabbits dying presented with similar symptoms.

In this paper will be presented the phenomenon or syndrome leading to death and its etiology considered.

### MATERIAL AND METHODS

Hybrid white rabbits of about 3 Kg. in weight were used. Following anaesthesia with intravenous Nembutal the animals were secured to the table. The femoral artery of one rabbit was joined to the femoral vein of the other rabbit of a pair and vice versa by siliconized plastic cannulae and the flow was regulated to a rate of 1.6 ml./min. by means of a rotary pump placed between the two circulations. The cannulae were removed after about two hours of cross circulation and the rabbits were followed up for varying periods, the longest period of observation being one year. Some of the rabbits were sacrificed at varying periods for pathological studies.

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外科学 (主任 教授 長石忠三)

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In addition, as a preliminary measure designed to find out to what extent admixture of the blood components were obtained in the rabbits of a pair, red cell tagging with  $\text{Cr}_{51}$  was done in one partner in some pairs and Evan's blue injected to one partner in other pairs before cross circulation.

Samples of blood were collected at intervals and the radioactivity or the dye density, respectively, was measured. It was found that within about two hours of cross circulation the red cells and the plasma were sufficiently evenly distributed between the partners. (Fig. 1 for  $\text{Cr}_{51}$  labelled red cells.)

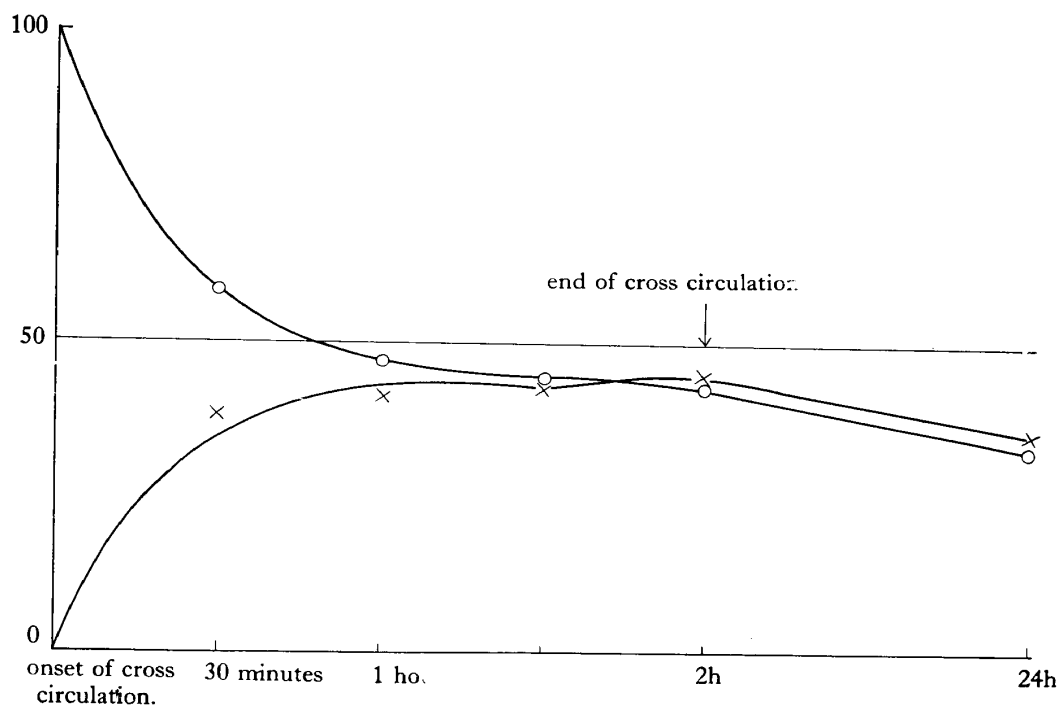


Fig. 1. Distribution of  $^{51}\text{Cr}$ -labelled Red Cells between Partners.

## RESULTS

Table 1 Survival Time after Cross Circulation.

Observation period	Total (pairs)	Pair which partners were both alive	Pair which one of the partners was dead and the other was alive	Pair which partners were both dead
1M or less	6	3 (50%)	3 (50%)	0
1M~3M	16	5 (31%)	9 (56%)	2 (13%)
3M~6M	8	1 (13%)	0	7 (87%)
6M or more	20	8 (40%)	11 (55%)	1 (5%)

## 1) Survival time.

Table 1 shows the survival times of the rabbits of the 50 pairs that were observed after being subjected to cross circulation.

Of the 50 pairs, there were 17 pairs or 34% in which both rabbits of a pair were alive during the period of observation while in 10 pairs or 20% both partners

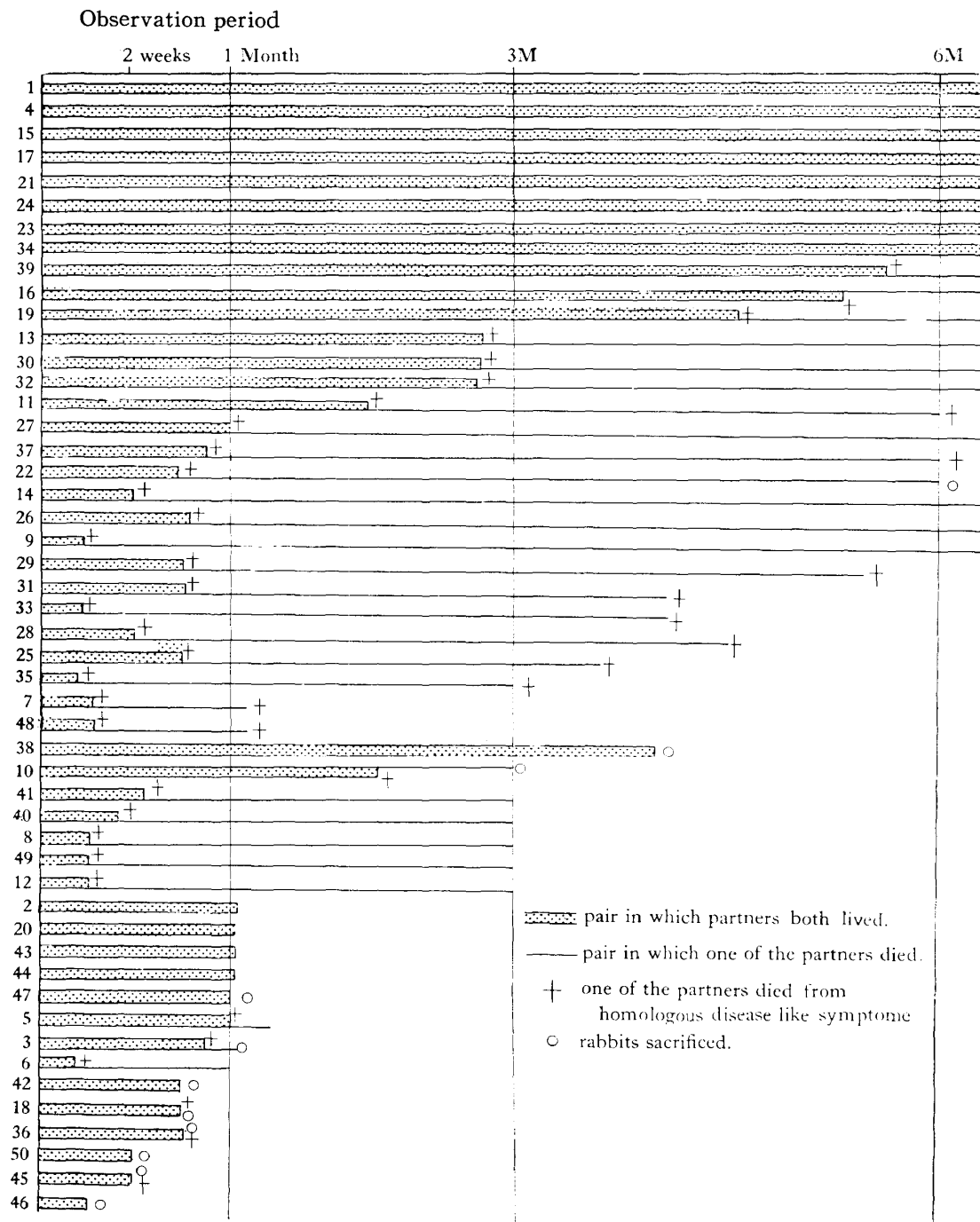


Fig. 2 Survival Time of Rabbits after Cross Circulation.

were dead and in 23 pairs or 46% one partner survived while the other died.

Through different periods of observation it was found that the incidence of cases where one partner of a pair died was fairly constant. (See column four Table 1.)

Pairs in which both partners were dead were greatest in pairs observed for three to six months and in most of these pairs one partner was dead within a month.

As shown in Fig. 2, the time of death after cross circulation varied for individual rabbits but all rabbits that died had sudden onset of diarrhoea, malnutrition revealed by reduction in body weight and erection of body hair, a few days before death.

In the control experiments in which either the blood from the femoral artery was circulated via the pump into the femoral vein of the same rabbit or blood transfusion (blood drawn and transfused with syringe) from one rabbit to the other of a pair and vice versa, no cases of death were observed.

## 2) Blood examination.

a) Leucocyte count (Fig. 3). Leucocytosis was seen on the first day after cross circulation but there was no difference between dying and surviving rabbits. However, as compared with rabbits in which transfusion was performed, the leucocytosis was marked in those in which the rotary pump was used for cross circulation or autocirculation. Within four weeks of observation there was no difference between rabbits subjected to cross circulation and the controls.

Also, leucocytosis was present in rabbits that died within one week after cross circulation but the symptoms seen before death were not affected by antibiotics.

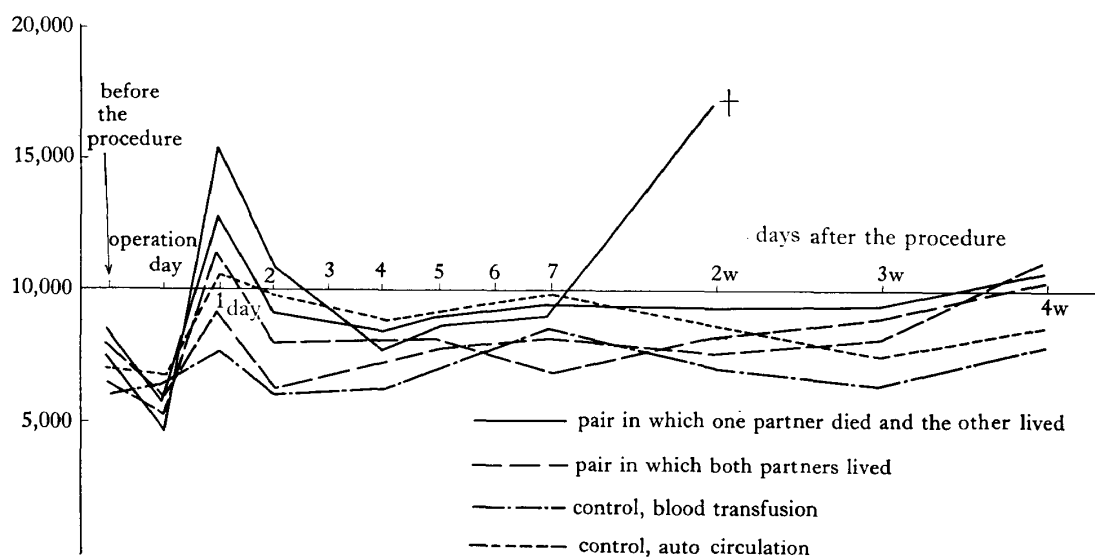


Fig. 3 White Cell Counts of Rabbits in Cross Circulation.

b) Erythrocyte count (Fig. 4). There was a 10 to 20% drop in the erythrocyte count starting immediately after cross circulation. Lowest counts were observed on about the fourth day and this was followed by gradual recovery. A similar phenomenon is seen clinically, after extracorporeal circulation.

c) Platelets (Fig. 5). There was a gradual reduction in the platelet count to about four days after cross circulation followed by a gradual recovery. Return to

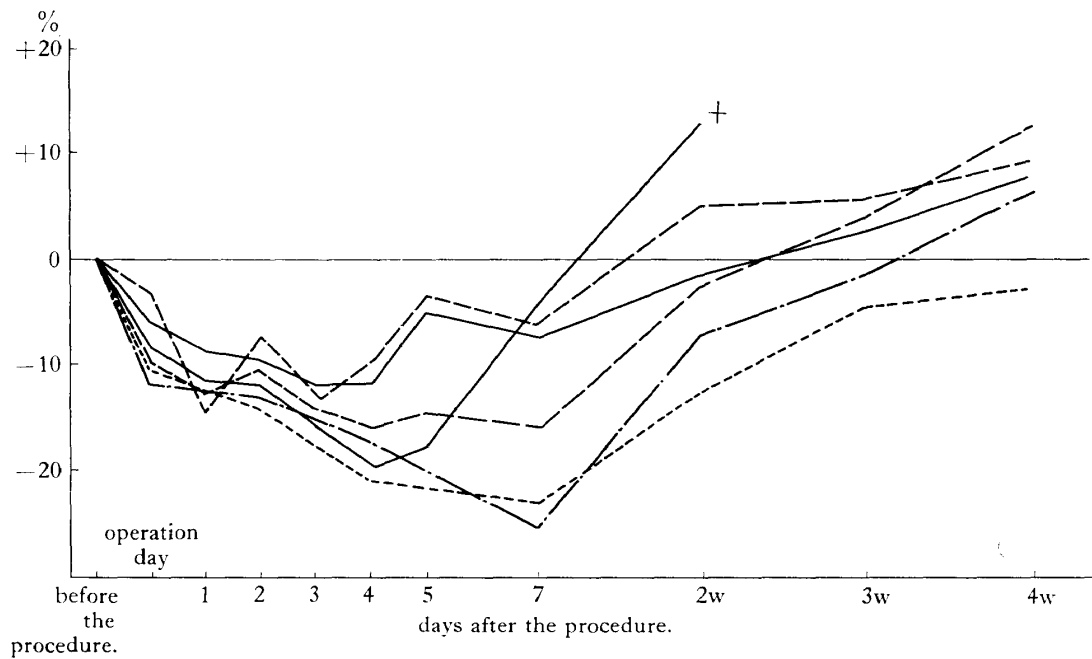


Fig. 4 Red Cell Counts of Rabbits in Cross Circulation.

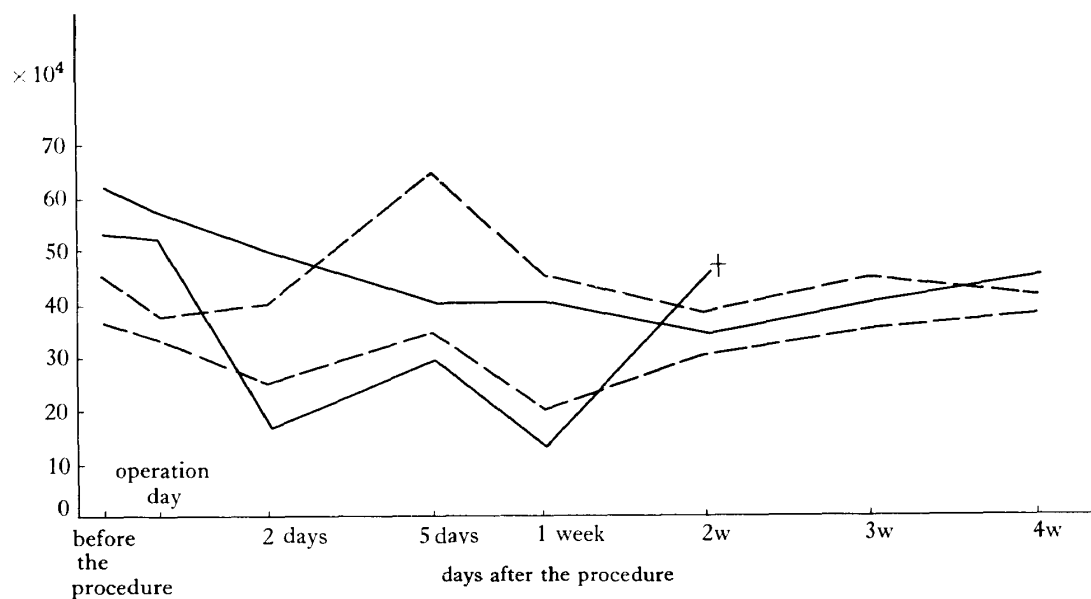


Fig. 5 Platelet Counts of Rabbits in Cross Circulation.

previous values was noted in two weeks. The changes in platelet count were similar in both dead and living rabbits.

d) Hematocrit (Fig. ). There was a gradual reduction in the hematocrit continuing to about the fourth day after cross circulation followed by gradual recovery and return to previous levels within two weeks.

e) Colour index (Fig. 7). There were no remarkable changes in the colour index in both controls and cross circulated rabbits though in the rabbits that died the colour decreased gradually and the rabbits showed hypochromic anaemia.

f) Differential count (Table 2). No marked changes were observed after cross circulation and especially no lymphocytosis was found from one to four weeks.

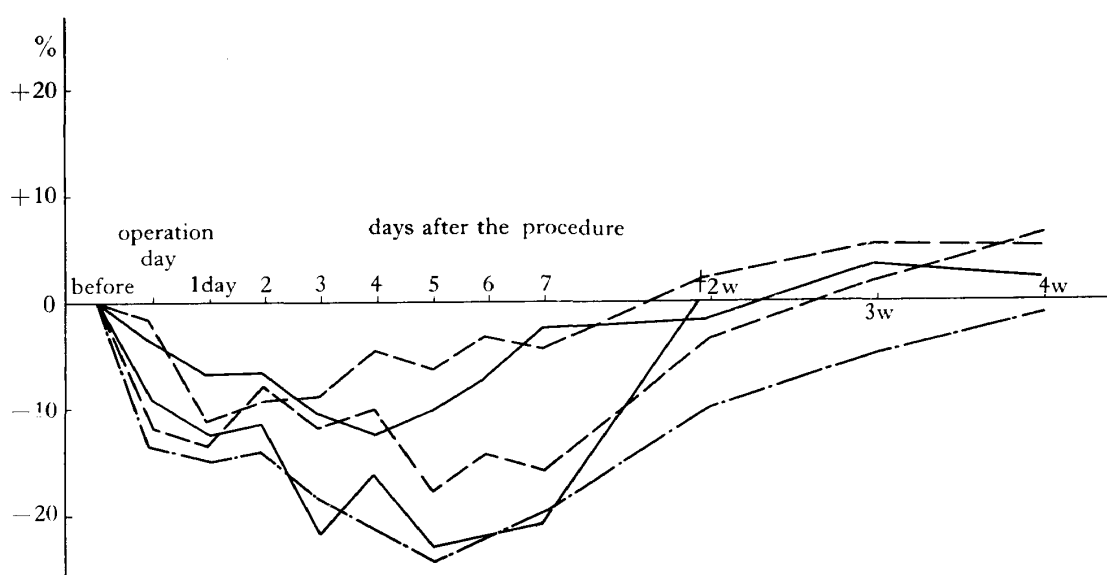


Fig. 6 Hematocrit of Rabbits in Cross Circulation.

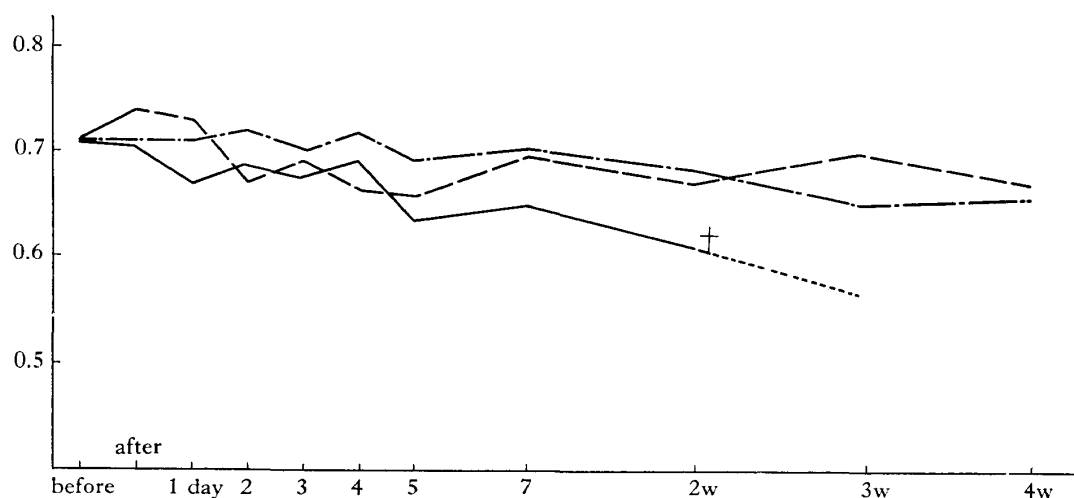


Fig. 7 Colour Index of Rabbits in Cross Circulation.

Table 2 Pre- and Post Operative Values of Leucocytes of Rabbits in Cross Circulation.

	Before the op .	3 days after the op.	1 week after the op.	2w	3w
Alive	Basophils 0%	14	0	2	0
	Eosinophils 2	0	3	0	0
	Bandforms 14	14	20	10	7
	PMN 22	30	43	46	33
	Lymphocytes 52	38	19	32	58
	Monocytes 10	4	15	10	2
Dead	Basophils		0		
	Eosinophils		0		
	Bandforms		15		
	PMN		30		
	Lymphocytes		33		
	Monocytes		22		
Control	Basophils 2	0	0		
	Eosinophils 0	0	0		
	Bandforms 12	3	2		
	PNM 11	30	8		
	Lymphocytes 70	62	82		
	Monocytes 3	4	5		

g) Plasma protein electrophoresis. From one to two weeks after cross circulation increases in alpha/ globulin or beta globulin were found but no changes in gamma globulin were seen.

### 3) Pathologic findings.

a) Macroscopic. The spleen of rabbits that died within one month was larger than normal while in those that died within three to six months appeared to be smaller than normal. Moreover, the thymus gland was on the average small. Neither hypertrophy nor atrophy of lymphatic could be recognized. (i.e. macroscopically).

b) Microscopic. Hemosiderosis of most organs, especially of the spleen, liver and kidneys, was seen microscopically. Also, atrophy of lymph node follicles and follicles of the spleen and areas of necrosis were seen.

## DISCUSSION

The injection of immunologically competent lymph node cells from the mature animal to the foetus just before birth, to the newborn, to X-irradiated animals, to F<sub>1</sub> hybrids etc. has usually interfered with normal growth and in the great majority caused death from within several weeks to several months. The diseases or syndro-



mes have been called runt disease, homologous disease, immunological disease, wasting disease, secondary disease, parabiotic intoxication etc. They represent a graft-versus-host reaction caused by the transfused cells. However, it is known that in the animals that survive some acquire a tolerant state. (Billingham, R.E. *Ann. N.Y. Acad. Sci.*, 73, 782, 1958.)

A similar graft-versus-host reaction can occur in a mature animal also, if large doses of the mature lymph node cells are repeatedly given.

Not only the lymph node cells, spleen cells, & thymus cells, but the lymphoid cells present in the peripheral blood are immunologically competent of causing such graft versus host reactions. It is said that the peripheral lymphoid cell plays the main role in homologous disease caused by transfusion of whole blood or buffy coat cells. (Cole & Garver, *Am. J. Physiol.*, 200, 147, 1961.)

With cross circulation, these peripheral lymphoid cells are transfused in continuous small doses but result in a large total dose. In half of the total pairs subjected to cross circulation, one of the pairs died; this together with the fact that the symptoms noted before death could not be controlled with antibiotics speak against the cause of death being due to infection including septicaemia. The sudden development of symptoms of diarrhoea, weight loss and erection of body hair followed by death in a few days is similar to situation observed in runt disease and homologous disease.

Also the syndrome following cross circulation differs from secondary disease and homologous disease in that there is no marked decrease in the leucocyte count and that there is no change in the lymphoid cells on the differential count.

The microscopic findings of atrophy of lymphatic tissue and necrosis in the spleen suggest that there might be some immunological reaction.

We have not, however, been able to find any positive evidence on immuno-haematological studies including Coomb's test, red cell resistance, antigen-antibody reactions (precipitation methods).

There are pairs of rabbits in whom both partners are quite normal and healthy six months after cross circulation. In some of these pairs skin grafting has been attempted and although it is too early to come to definite conclusions it seems that in some cases the grafts have survived longer than usual. Whether it is due to the fact that the rabbits may have originally been histocompatible or whether it is due to tolerance induced by cross circulation, we cannot as yet clarify but the findings are in agreement with those clinical signs in cross circulation as reported by Esbach et al., (*New Eng. J. Med.*, 273, 997, 1965).

As the animals used in these experiments were rabbits and the fact that they

were not inbred may have been one cause for not obtaining the picture of a typical graft-versus-host reaction. It is hoped to use an inbred strain for further studies. Another problem is to find a method for judging this syndrome by tests based on immunological methods.

Anaemia in the peripheral blood is seen in secondary disease and homologous disease and in this respect the syndrome following cross circulation resembles these diseases. (Cole & Garver, *Int. J. Rad. Biol.*, 2 309, 1960.). But this anaemia was also seen in the rabbits that had blood transfusions as well as in those subjected to autocirculation, and is seen with extra-corporeal circulation in man. It is unlikely that the anaemia following cross circulation is a manifestation of an immunological reaction.

Similar syndromes are also described by Hechtman et al. (Hechtman, H.B., Blumenstock, D.A., Thomas, E.D. and Ferrebee, J.W. *Surgery*, 52: 810, 1962).

Their report indicates that in dogs subjected to cross circulation, a late death from a secondary syndrome has occurred frequently in one of the partners when the partner was treated with immunosuppressive drugs or sublethal radiation.

### **SUMMARY**

1. Cross circulation between pairs of white mature rabbits was performed. Disregarding the time of death, one partner of most pairs died after cross circulation and in all the rabbits that died similar symptoms consisting of sudden onset of diarrhoea, erection of body hair, weight loss etc. were seen and death took place within a few days after onset of these symptoms.

2. This syndrome was clinically similar to homologous disease in some respects, but several points of difference were noted and demand further study.